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Design and synthesis of new octadentate macrocyclic chelators for ^{89}Zr

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Introduction

^{89}Zr is one of the most interesting radiometals for Positron Emission Tomography. This radionuclide possesses a low energy β positron which affords high resolution images, and a half life of 78.41 h, allowing a collection of images several days after injection, making this isotope particularly suitable for labelling biomolecules with long biodistribution time such as antibodies [1]. The most commonly used chelator for^{89}Zr is Desferrioxamine (DFO) but one drawback of this latter is the partial decoordination of the metal in vivo. The challenge is to encapsulate ^{89}Zr to avoid release in organs while keeping good properties for molecular imaging.

Methods

Our concept uses macrocyclic polyamines as platforms to attach two kinds of coordinating moieties, i.e. picolinic acid and hydroxyquinoline. Four macrocycles were used: cyclen, cyclam, TACN and 13(ane)N4. The cycles were functionalized by addition of a p-nitrobenzyl group to allow further bioconjugation. Radiolabelling of some chelators with ^{89}Zr and competition experiments with DTPA were performed.

Results

8 new chelators were synthetized and metallated with $Zr(acac)_4$. The macrocycles and the corresponding complexes were characterized by ESI, UV and NMR spectroscopies. Radiolabelling of 3 chelators with ^{89}Zr confirmed their promising coordinating properties. Competition with DTPA showed no transchelation for several days especially with the cyclam derivatives. DFT calculation had shown that the chelators are adapted to the complexation of Zr.

Conclusions

New macrocyclic chelators containing both pendant coordinating arms and a function for bioconjugation were prepared and characterized. The synthesis can be easily scaled-up. The first results showed that these chelators could be an alternative to DFO.

References

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